REMARKS

Applicants request reconsideration of the present application in view of the foregoing amendments and following remarks.

I. *Status of the Claims*

Claims 21-24 and 39-103 are pending. Claims 21-24, 39, 40, 42, 46, 47, 49, 50, 51, 55, 56, 58, 62, 63, 65-67, 71, 73, 75, 79, 80, 82-84, 88, 89, 91, 95, 96 and 98-100 have been amended to delete hydrogen and/or (C_1-C_8)-alkyl from the definition of R^0. Applicants, however, reserve their rights to file a divisional application in respect of the subject matter deleted from these claims. These amendments do not constitute acquiescence in the propriety of any rejection made by the Examiner, but are made merely to further the case toward allowance.

II. *Rejection of Claims 21-24 and 39-103 under 35 U.S.C. §103(a)*

Claims 21-24 and 39-103 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,424,293 to Zoller *et al.* ("Zoller"). Applicants respectfully traverse this rejection.

The Examiner alleges that the instant claims differ from the reference by reciting specific species and/or a more limited subgenus than the reference. However, applicants wish to point out that the pending claims 21-24 and 39-103 are directed to a method of treatment based on use of compounds of the present invention as VLA-4 receptor antagonists, but are not directed to compounds per se. Thus, while the Examiner has provided an extensive explanation of the genus-species relationship between compounds of the prior art and the compounds recited in claims 21-24, because claims 21-24 and 39-103 are simply not compound claims, this reasoning is not applicable to the present case.

The Examiner also alleges that one having ordinary skill in the art would have been motivated to select "the claimed compounds" from the genus in the reference to prepare additional beneficial preparations and method of use because such compounds would have been suggested by the reference as a whole.

At first, applicants note that claims 21-24 have been amended herein to delete denotations, hydrogen and $(C_1$-$C_8)$-alkyl, from the definition of group R^0. Group R^2 in the formula (I) of Zoller, corresponding to group R^0 in the formula (I) of the present invention, is defined to include hydrogen and $(C_1$-$C_8)$-alkyl, only. Thus, the compounds recited in the amended claims 21-24, in which R^0 is, for example, cycloalkyl, cycloalkyl-akyl, aryl, aryl-alkyl an acyl group or a sulfonyl group, are structurally remote from the compounds disclosed in Zoller. Accordingly, there is no longer genus-species relationship between the compounds recited in claims 21-24 and compounds of Zoller. Furthermore, contrary to the Examiner's assertion, considering such a distinctiveness in chemical structure, it should be immediately apparent to the Examiner that one of ordinary skill in the art would not have been motivated to use the compounds of the present invention for the methods of claims 21-24, without hindsight benefit of knowing from the present specification that they possess VLA-4 antagonizing activity, the activity upon which all of the pending claims are based.

Zoller discloses that their compounds possess the ability to inhibit cell-cell adhesion which is due to the interaction of Arg-Gly-Asp (or RGD)-containing proteins, such as fibronectin, fibrinogen or the von Willebrand factor, with the so-called integrins. Vitronectin, collagen and laminin are additionally disclosed as other adhesive proteins which are inhibited to bind to the corresponding receptors by the compounds of Zoller. See column 12, lines 21-33. Vitronectin, as confirmed from the specification, page 1, lines 5-6 of the second paragraph, also contains RGD sequence that interacts with integrins.

In contrast, the instantly claimed invention is based on the finding that compounds of the present invention surprisingly inhibit interaction of ligands with integrin VLA-4. VLA-4 inhibitory activity of the present invention is demonstrated in the test results shown at page

94, line 28 to page 95, line 28. As explained in the specification, VLA-4 antagonism used in the methods of claims 21-24 is clearly different than the adhesion inhibition as disclosed in Zoller. Specifically, the integrin VLA-4 is distinct in that it interacts with an **LDVP** sequence, while the fibrinogen or vitronectin receptor, binding of which is inhibited by the compounds of Zoller is a typical type of **RGD**-binding integrin. See page 2, lines 4-7 of the specification. Thus, one of the important ligands of VLA-4, VCAM-1, does not contain an RGD sequence. See page 2, lines 14-15 of the specification. Furthermore, VLA-4 is atypical in so far as its interaction with other cells is mainly restricted to lymphoid and myeloid cells while the fibrinogen and vitronectin receptor interact with fibrinogen or vitronectin. See page 1, last line to page 2, line 2. The difference in the mode of action of other integrins from VLA-4 is distinct because VLA-4 is chiefly responsible for lymphocyte adhesion to vascular endothelium and leukocyte recruitment to the inflamed area whereas fibrinogen or vitronectin cause platelet aggregation or osteoclast binding to the bone surface. Thus, antagonism of VLA-4 is useful for the treatment of diseases caused at least partially by an undesired extent of leucocyte adhesion and/or leucocyte migration or are associated therewith, for example, inflammation, rheumatic conditions, asthma, allergies, while antagonism of fibrinogen receptor is effective for the treatment of diseases caused by blood platelet aggregation or adhesion of fibrinogen to blood platelets, for example, thrombosis.

However, Zoller fails to recognize if their compounds might exhibit VLA-4 antagonistic activity, let alone fails to teach or suggest such an activity. Thus, one of ordinary skill in the art would not expect that compounds of the present invention would exhibit VLA-4 antagonistic activity from the disclosure of Zoller, and therefore can be used in the methods of treatment as claimed in claims 21-24. Accordingly, inhibition of interactions between VLA-4 and ligands containing LDVP, not RGD, by using compounds of the present invention is itself an unexpected result relative to the disclosure of Zoller. Furthermore, such unexpected results could not have been predicted on structural analysis of the compounds of Zoller and, accordingly, would be considered surprising to one of ordinary skill in the art.

The attainment of unexpected results or properties is a powerful demonstration of patentability. *See U.S. v Adams*, 383 U.S. 39, 51-52 (1966); *Lindemann Maschinenfabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir 1984). Applicant's demonstration of unexpected results further establishes patentability of the claimed invention.

Quite apart from the complete lack of motivation, the prior art would not have enabled one of ordinary skill in the art to carry out the presently claimed treatments. Given only Zoller's data on fibrinogen receptor activity, one of ordinary skill in the art certainly would not have been enabled to carry out the instantly claimed methods which are based on the present specification's showing of VLA-4 receptor antagonism.

Accordingly, withdrawal of the rejection is respectfully requested.

In addition, according to the request of the Examiner, applicants submit that the support of the method as claimed in the specification can be found at pages 29, last paragraph to page 30, first paragraph, as well as page 4, third paragraph to page 5, first paragraph.

In view of the above amendments and remarks, favorable reconsideration and allowance of the application are requested. In the even that any issues remain, the Examiner is invited to telephone the undersigned with any proposal that would further expedite prosecution.

Respectfully submitted,

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